### **DEPARTMENT OF HEALTH & HUMAN SERVICES**



Food and Drug Administration Center for Biologics Evaluation and Research Office of Compliance and Biologics Quality Division of Manufacturing and Product Quality

To: Thomas Finn, Ph.D., Microbiologist, OCTGT/DCGT/CTB, HFM-720

File STN 125197/0/034 and STN 125197/0/045

From: Gang Wang, Ph.D., Biologist, OCBQ/DMPQ/MRB II, HFM-676

cc: Lori Tull, CSO, OCTGT/RMS, HFM-705

Through: Chiang Syin, Ph.D., Branch Chief, OCBQ/DMPQ/MRB II, HFM-676

Subject: Review Memo of the Class 2 Response to CR Letter Submitted by Dendreon to Seek

Licensure of Sipuleucel-T for the Treatment of Men with Asymptomatic, Metastatic

Androgen Independent Prostate Cancer

#### RECOMMENDATION

Based on the information submitted in this Class 2 Response to CR letter (STN 125197/0/034), Amendment (STN 125197/0/045) and the sponsor's satisfactory responses to my review and inspectional questions, I recommend an approval to this BLA.

### ADDITIONAL COMMENTS

During the Pre-licensing Inspection (PLI) conducted by CBER at Dendreon's manufacturing facility at Morris Plains, NJ on January 25 - 29, 2010, the inspectors discovered that since the submission of the current amendment (STN 125197/0/034), the sponsor has installed and implemented a ------(b)(4)----- software system and a ------(b)(4)----- system, which were not included in the current amendment. In addition, the ---(b)(4)---- for the HVAC system, which have been in service since 2007, were neglected to be included in the BLA.

The ----(b)(4)----- system is a comprehensive and sophisticated software that was specifically designed for scheduling, manufacturing and distribution of Dendreon's commercial product. Since the implementation of the ----(b)(4)----- system, the sponsor has been heavily relying on the system for their daily operations.

----(b)(4)----- was added to the manufacturing facility air system in 2007 prior to the 2007 PLI. However, due to an oversight, the change was not included in subsequent amendments to the BLA. ------(b)(4)------ were added to ----(b)(4)----- (serving cleanroom Modules --

(b)(4)) and(b)(4) (serving the product and non-product corridors). The units were commissioned and validated in 2007.
Subsequent to the submission of BLA Amendment 034, Dendreon has re-modified the(b)(4) system for the cleanroom and QC lab incubators by replacing the existing(b)(4)(b)(4)
for the phased expansion of the NJ facility currently under(b)(4) construction.
During the 2010 PLI, I have verified the documentations associated with the installation and qualification/validation of the new(b)(4) system,(b)(4)
The information for the(b)(4) system has since been submitted in a BLA amendment (STN 125197/0/043) and has been evaluated by the software expert in the product office. The initial review indicates that the system is acceptable. During the 2010 PLI, I verified the documents related to the qualification/validation of the(b)(4) system. From a regulatory perspective, the system was adequately validated, implemented and documented. No major deficiencies were noted. More detailed information can be found in my EIR and software review memo.
The documentations related to the(b)(4) were initially reviewed during the 2007 PLI and verified during the 2010 PLI and were deemed acceptable. Dendreon has submitted a BLA amendment (STN 125197/0/045) on March 26, 2010 to include the(b)(4) to their NJ facility.
On March 26, 2010, Dendreon submitted an Amendment 045 describing the(b)(4)

(		

### **REVIEW SUMMARY**

#### Introduction

Dendreon Corporation (Dendreon) submitted their original BLA (STN 125197/0) on November 13, 2006 for sipuleucel-T (Provenge®) for the treatment of men with asymptomatic, metastatic androgen independent prostate cancer (ACIP). A PLI was conducted on February 12 – 16, 2007 at Dendreon's manufacturing facility located in Morris Plains, New Jersey. A Complete Response (CR) letter concerning some clinical, CMC and inspectional deficiencies was subsequently issued to the sponsor on May 8, 2007. My previous review memo recommending a CR letter to the original BLA was signed off by Dr. Chiang Syin on April 27, 2007.

On October 30, 2009, Dendreon submitted a Class 2 Response (STN 125197/0/34) to address the deficiencies listed in the CR letter. Because the last PLI was conducted in almost three years ago in February 2007 and the facility has not been re-inspected since then, CBER decided to conduct a reinspection at sponsor's NJ facility on January 25 – 29, 2010. Details of this inspection are documented in the EIR.

In their response to my requests made during a Type C meeting dated June 5, 2009, Dendreon also provided information regarding the changes that have been made at the NJ facility since the 2007 PLI. These items are presented in the following pullet points. Detailed review of the facility, utility, equipment and manufacturing processes can be found in my previous BLA review memo (STN 125197/0) dated April 13, 2007.

- A summary of environmental monitoring data.
- Changes to the functional spaces in the NJ facility. This section includes an overview of
  physical changes in manufacturing support areas. The sponsor states that these changes
  will be completed by January 2010. Projects currently in progress may require additional
  modifications; therefore, the descriptions provided herein cannot be considered all
  inclusive. All such modifications are managed under Dendreon's change control
  procedures.
- New equipment in the QC laboratory and elsewhere in the facility.
- Revisions made to the sipuleucel-T manufacturing batch record. No changes have been made to the manufacturing process, but changes in formatting and organization of the document have occurred.

In addition, the sponsor provided updated facility drawings. The building is currently the subject of an on-going phased construction plan. The conceptual plans for the facility expansion were

discussed with CBER at a teleconference on January 15, 2009. The changes that have been made or to be made to the existing facility are not the subject of this review and will be submitted as supplements to the BLA in future after the BLA is approved.

•	(b)(4)
	<del></del> ,
•	
	(b)(4)
	(b)(4)

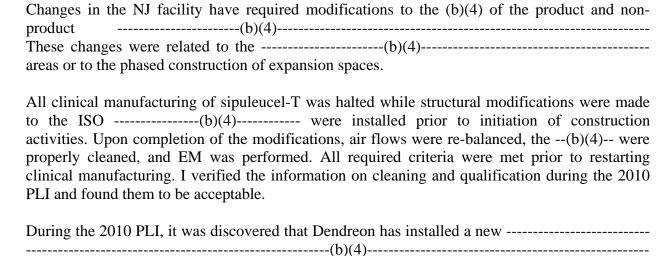
## **Environmental Monitoring**

Reports are produced quarterly and annually, to summarize and analyze the routine and inprocess EM results obtained at the NJ manufacturing facility. The annual reports for 2007 (TR 30616) and 2008 (TR 30645) are provided. These reports include summary tables, trend charts, and characterization of local isolates. Two quarterly reports are provided to address the on-going environmental monitoring for 2009: January 1st – March 31st 2009 and April 1st – June 30th 2009. The quarterly reports contain data similar to the annual reports but with limited analysis of those data. I have reviewed the EM summary reports and found them to be acceptable. The EM summary reports and trending analyses were further verified during the 2010 PLI. No major issues were noted.

### **Changes to Functional Spaces**

Since CBER's 2007 PLI at the NJ facility, several changes have been made to the manufacturing support areas. These changes are summarized in the following table. Most facility changes have had little or no impact on --b(4)------- One set of changes included activities that impacted the outer corridors of ----b(4)------ area. These changes are discussed in more detail in Section of Facility Changes in Manufacturing Corridors. A complete set of updated facility drawings is provided and reviewed. No major concerns were noted.

2 Pages determined to be not releasable: (b)(4)



------ facility, but the relevant information was not submitted in the BLA amendment. They have done the IQ/OQ of the system and qualified the  $_{(b)(4)}$  and I have reviewed the documents. No major concerns were noted. I requested that the relevant information be submitted as an amendment (STN 125197/0/045) to the BLA.

# **New QC Lab Equipment**

As requested at the June 5, 2009 Type C meeting, Dendreon has provided information on the new QC lab equipment that has been added to the NJ facility since the 2007 PLI.

-----(b)(4)----------(b)(4)-----------(b)(4)-----------(b)(4)-----------(b)(4)-------

The new QC equipment was qualified and/or calibrated as required. During the 2010 PLI, the inspection team verified the qualification of the newly added QC lab equipment. No major deficiencies were noted.

#### **Master Batch Record Revisions**

An unexecuted copy of the sipuleucel-T master batch record, BR 45025, was provided in BLA 125197, Original Submission. The batch record has been modified to clarify some steps and to provide better process control at some points. The manufacturing procedures remain the same. The revisions to the batch record do not alter the basic steps used to produce sipuleucel-T, i.e., cell manipulations, buoyant density separations, ex vivo culture, harvest, and formulation. Table 3 (not included in this review memo) presents an overview of the revisions made to the sipuleucel-T batch record since the 2007 PLI. Items requiring additional explanation are further addressed following the table. Unique modifications have been categorized as key changes. Some changes were related to multiple steps throughout the batch record, and these have been categorized as general changes. A number of formatting changes have also been made for

clarification purposes. I would defer the evaluation of the revisions made the master batch record to product reviewers.

Automated Calculations						
In-process(b)(4) Results						
b(4)						

h:\bla reviews\dendreon bla stn 125197.0\amendment 103009\review\dendreon bla stn 125197.0.34 class 2 resubmission.doc